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The question of the precise role of the heart in shock has been largely unresolved. Previous separate reports have shown that both excitatory and depressant actions on the myocardium after endotoxin are observed. The purpose of the present study was to assay the possibility of a direct myocardial toxic action of endotoxin or a circulating myocardial depressant factor released in the blood of endotoxin shocked animals. This was accomplished by utilization of beta adrenergic blockade (propranolol) under the experimental conditions of constant cardiac output and aortic pressure in an isolated canine heart preparation exchanging blood with an intact support animal shocked by endotoxin.

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EFFECTS OF ENDOTOXIN ON MYOCARDIAL HEMODYNAMICS, PERFORMANCE AND METABOLISM DURING BETA ADRENERGIC BLOCKADE

L. B. Hinshaw, L. J. Greenfield, L. T. Archer, C. A. Guenter

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The question of the precise role of the heart in shock has been largely unresolved (1). Although it is generally agreed that the heart will ultimately fail in shock, its possible contributory role in the development of irreversibility is in serious question. A prevailing view is that the heart is one of the first organs to fail in shock (2-5). Solis and Downing found that ventricular contractile force was diminished after endotoxin even when arterial pressure was maintained (6). Lefer and others have identified a myocardial depressor substance (MDF) in the plasma of animals in hemorrhagic or endotoxin shock (7-10). They have postulated that this factor may perform an important role in the pathogenesis of irreversibility by depressing excitation-contraction coupling or by impairing the cardiac machinery directly (8). It is a possibility that MDF is a toxic substance gradually released by some ischemic organ or is a normally occurring metabolite which accumulates in the plasma and reaches toxic concentrations (7). On the other hand, Goodyer found that ventricular contractile capacity was enhanced in endotoxin shock as a result of increased sympathetic drive (11), and current studies carried out in this laboratory have failed to demonstrate a direct cardiotoxic influence of endotoxin (12). It is conceivable that a cardiodepressant action of endotoxin could be masked by a simultaneous myocardial stimulating action of catecholamines released as a result of systemic hypotension. The present study was devised to explore this possibility by the utilization of pharmacological doses of a beta adrenergic blocking agent. Results from the study fail to reveal a myocardial depressant effect following a lethal injection of endotoxin. Cardiac performance was unimpaired after endotoxin in the presence of beta adrenergic blockade.

/

MATERIALS AND METHODS

Experiments were carried out on adult mongrel dogs intravenously anesthetized with sodium pentobarbital, 30 mg/kg. The basic procedure was to support an isolated left ventricle by blood exchanged with a heparinized support animal. The donor heart dog was anesthetized, and the [illegible] opened [illegible] by [illegible] the animal was placed on a constant volume respirator. The azygous vein and subclavian artery were ligated and divided. Ligatures were loosely placed around the thoracic aorta distal to the subclavian artery, the brachiocephalic artery, and superior and inferior vena cavae. The pericardial sac was opened along its ventral surface and the animal was heparinized (3-5 mg/kg). The vagi were then cut in the neck and the brachiocephalic artery was cannulated with a tygon tube elevated to a height of 100-125 cm above the heart level. The superior vena cava was cannulated with a blood filled plastic tube led through a roller-type blood pump prepared to draw blood from the aorta of the support dog. Blood was allowed to flow through the brachiocephalic cannula and to fill the tygon tube. The purpose was to provide an adequate hydrostatic pressure for coronary perfusion and to allow the transfer of the heart to the external perfusion system without interruption of coronary flow. The aorta of the isolated heart was then tied distal to the origin of the brachiocephalic artery, the superior veral caval inflow from the pump was commenced at about 120 cc/minute, and the inferior vena cava was immediately ligated. Blood from the aortic outflow of the isolated heart was collected in a plastic reservoir (Figure 1) and returned to the dog at a flow rate equal to the superior vena caval inflow. The heart and lungs were then removed from the chest and supported by the trachea in the external system with adequate coronary pressure and flow constantly provided. The lungs of the isolated heart were not ventilated, and the support animal was respiring spontaneously.

A strain gauge arch was sutured under stretch to the lateral wall of the left ventricle for measurement of myocardial contractile force in some experiments (13). Left ventricular pressure was measured simultaneously for end diastolic pressure (0-40 mmHg), and systolic pressure (0-200 mmHg) by means of separate Statham pressure transducers attached by a "Y"-connector to a plastic cannula inserted through a purse string suture in the apex of the left ventricle.

The right heart was then bypassed after first placing a saline filled plastic tube into the right ventricle via the atrium, and then cannulating the pulmonary artery from a "T" connector previously secured to the superior vena caval inflow tubing. The cannulation of the pulmonary artery required only a few seconds during which time the coronary vessels were retrograde-perfused with blood by hydrostatic pressure from the aortic outflow tubing. Coronary venous blood was collected from the right ventricular drain into a plastic reservoir and returned together with brachiocephalic outflow to the support dog via a second pump. Cardiac output was taken as the sum of aortic outflow and coronary flow, both measured with a cylinder and stop watch. Temperature of coronary venous blood was monitored with a temperature probe. Aortic pressure, left ventricular pressures, cardiac contractility and ECG of the isolated heart, and systemic pressure of the support animal were monitored continuously on a Sanborn recorder. The first derivative of the left ventricular pressure, dP/dT_{max}, was also continuously recorded by means of a resistance-capacitance differentiating network. Mean aortic pressure and cardiac output were increased steadily in the isolated heart preparation by adjustment of a screw clamp on the aortic outflow and elevation of pump speed supplying the pulmonary artery. An Instrumentation Laboratories blood gas analyzer was utilized for coronary arterial and venous pH determinations.

Oxygen content of coronary arterial and venous blood was measured by a Van Slyke manometric blood gas analyzer. Simultaneously obtained coronary blood flow measurements permitted the calculation of oxygen uptake and carbon dioxide production from the product of coronary flow and A-V oxygen or carbon dioxide differences.

During the equilibration period of the isolated heart preparation, aortic pressure was stabilized at an average of 107 mmHg with a cardiac output of 76 cc/min/kg body weight (based on the weight of the heart donor dog). These pressure and flow values supported and maintained left ventricular systolic and diastolic pressure, coronary blood flow, and myocardial oxygen uptake in the physiological range, and were maintained during the entire experiment by screw clamp adjustment on the left ventricular outflow tubing and by maintaining a constant pulmonary arterial inflow.

Stroke work in gram-meters was calculated from the formula used by others (14):

$$(MAP - LVEDP)\ (SV)\ (1.36)/100$$

where MAP = mean aortic pressure (mmHg); LVEDP = left ventricular end diastolic pressure (mmHg) and SV = stroke volume in cc, determined by dividing cardiac output by heart rate. The acceleration component of left ventricular stroke work was disregarded in the calculations on the basis that it represents less than 1 per cent of total stroke work (15). Cardiac power was calculated and expressed as work per second. The maximum change in pressure (dP/dT_{max}) occurring during isometric contraction of the left ventricle (14, 16) was continuously recorded and expressed as the first derivative of the pressure rise. Calibration of the dP/dT recording was carried out by analysis of the slope of a line drawn tangentially to the steepest portion of the left ventricular isovolumetric tracing and

expressed as mmHg/sec (17). Oxygen uptake was assumed to be negligible in atria and right ventricle (bypassed) as was reported by others (18). Propranolol, 0.5 mg/kg, was infused during a fifteen minute period in a volume not exceeding 20 ml. The degree of beta adrenergic blocking characteristics was assayed by intracardiac injections of epinephrine or isoproterenol and blockade was essentially complete for chronotropic, inotropic and coronary vasodilatory responses to injected epinephrine. Blockade was evaluated periodically during the total course of the experiments. At the end of the control period, and LD_{90} of E. coli endotoxin, 1.2 mg/kg (Difco, Detroit), based on the weight of the dog providing the heart was injected into the pulmonary arterial inflow of the isolated heart. An additional amount of endotoxin based on the weight of the intact table dog plus the weight of the isolated heart and lungs minus the amount injected directly into the isolated heart system, was intravenously administered to the intact support animal. Animals providing the isolated heart averaged 5.5 kg while intact support animals were 20.5 kg in average weight. All dogs were mature adult animals.

RESULTS

Figure 2 illustrates the typical effects in a single experiment, of beta adrenergic blockade before and after endotoxin, on the inotropic, chronotropic and coronary hemodynamic responses of the isolated heart to epinephrine. In general, all experiments demonstrated that a dose of intravenously administered propranolol of 0.5 mg/kg body weight was sufficient to produce nearly complete beta adrenergic blockade of the isolated heart. Intracardiac injections of epinephrine or isoproterenol of 0.5 micrograms resulted in significant positive inotropic and chronotropic cardiac responses, and increased coronary blood flow, prior to propranolol administration. After beta adrenergic blockade, and uring the total course of the present experiments, these three types of cardiac responses were essentially abolished to 10-20 microgram injections of catecholamines.

Table I shows the effect of an LD_{90} injection of endotoxin on the intact support dog, supplying blood to the isolated heart, following beta adrenergic blockade. Mean systemic arterial pressure and heart rate decreased after propranolol injection, and fell significantly lower during a two hour period after endotoxin injection.

In order to assay the effects of endotoxin on myocardial performance and metabolism, it was essential that certain parameters were controlled, and these are shown in Table II. It is seen that mean aortic pressure (coronary pressure) and cardiac output of the isolated heart were maintained relatively constant. Coronary blood temperature fell somewhat in spite of artificially imposed warming procedures because of the profound hypothermia developed in the severely shocked support animal. This degree of temperature depression in the perfusion medium of the isolated heart, however, did not appear to exert a significant decremental influence on myocardial metabolism.

Hemodynamic responses of the isolated heart during constant cardiac output and mean coronary perfusion pressure, are illustrated in Table II. Beta adrenergic blockade did not significantly alter coronary blood flow or coronary vascular resistance ($p > 0.01$). Mean flows and resistances, however, were markedly changed after endotoxin injection ($p \leq 0.05$), Coronary blood flow steadily increased to double the control value ($p < 0.05$), 50-125 minutes post-endotoxin, while coronary vascular resistance progressively fell to approximately fifty percent of the pre-endotoxin value ($p \leq 0.05$, 50-125 minute period).

The effects of an LD_{90} endotoxin on cardiac performance following propranolol are shown in Table III. Left ventricular end diastolic rpessure (LVEDP), dP/dT, and cardiac power (work/sec) were unaltered by propranolol administration prior to endotoxin injection. Heart rate reduction resultsd in a rise in stroke work since cardiac output, "after load" (aortic pressure) and "pre-load" (LVEDP) were relatively unchanged. During the two-hour period after endotoxin, VVEDP, dP/dT, and power remained unchanged while a progressively developing bradycardia from 125 to 100 beats/minute resulted in gradually raising stroke work from a mean of 4.9 to 6.4 gm·meters.

Finally, pH and oxidative metabolic parameters were studied in the isolated heart and results show no significant alteration in oxygen uptake ($p > 0.10$) although a decrease in carbon dioxide production is observed within one hour after endotoxin injection (Table IV). Coronary arterial and venous pH are significantly lowered during the entire post-endotoxin period ($p \leq 0.05$). Propranolol administration exerted no notable effect on pH, oxygen uptake and carbon dioxide production prior to endotoxin injection.

Figure 3 is a representative experiment demonstrating the absence of a deleterious effect of endotoxin on cardiac hemodynamics, work performance and metabolism during beta adrenergic blockade.

DISCUSSION

The experimental evaluation of a possible direct detrimental action of endotoxin on the myocardium is a difficult complex problem. Venous return has been demonstrated to fall after endotoxin in both canine and primate species and sufficient information is available to account for the subsequent drop in cardiac output entirely on the basis of peripheral, extracardiac factors (19-22), during the early phase of shock. The present study, a recent report (12), and parallel work carried out in this laboratory provide evidence for the absence of a direct toxic action of endotoxin on the myocardium. Even though all support animals were severely damaged from the effects of endotoxin in the current series, as exhibited by extremely low arterial pressures and deaths occurring within three hours, isolated hearts performed normally as shown by cardiac work and power, dP/dT, LVEDP and oxygen uptake.

Goodyer (11) pointed out that ventricular contractile capacity was enhanced in hemorrhagic and endotoxin shock as a result of increased sympathetic drive. Lefer and others, on the other hand, demonstrated the release of a cardiodepressant blood borne factor in hemorrhagic and endotoxin shock (7-10). It seemed conceivable to us that both the excitatory and depressant influences could be operative in endotoxin shock and tended to cancel each other's effects. However, results from the present study show that with the elimination of sympathetic influences on the heart by beta adrenergic blockade, which would be expected to unmask a depressor effect, there is no evidence of a circulating cardiodepressant factor in the blood of animals dying in irreversible shock. Cardiac performance appeared to be well maintained in part at least by increased coronary blood flow and decreased pH which should increase oxygen delivery to myocardial tissue (23). The increase in coronary blood flow

could not have been due to catecholamine release sine this action was clearly blocked by propranolol. Key factors in the mechanism of increased coronary flow in the present study are probably myocardial tissue, oxygen tension and circulating vasodilator metabolites (23). Thus, increased myocardial blood flow, achieved by marked coronary vasodilatation coupled with adequate extraction of oxygen from capillary blood, and the ability of the heart to achieve normal oxidative metabolism in a relative acid medium, provide the necessary essential ingredients for normal myocardial performance.

Results fomm the present study are in agreement with Weil and others who found no electrocardiographic evidence for myocardial failure after endotoxin (19); Londe and others (24) who observed that endotoxin produced no perceptible effect on myocardial extraction of oxygen; Kutner and Cohen who reported that lethal loses of endotoxin did not affect myocardial contractility (25); and Alican and others who noted a resistance of the myocardium to endotoxin when arterial pressure is maintained (26).

Findings from the present study do not preclude the possibility of adverse effects of prolonged systemic hypotension and progressive peripheral pooling on cardiac performance which most assuredly occur. The data clearly suggest, however, that myocardial performance is not damaged by direct or secondary toxic effects of endotoxin or myocardial depressant substances, circulating in the blood of irreversibly shocked animals.

SUMMARY

The question of the precise role of the heart in shock has been largely unresolved. Previous separate reports have shown that both excitatory and depressant actions on the myocardium after endotoxin are observed. The purpose of the present study was to assay the possibility of a direct myocardial toxic action of endotoxin or a circulating myocardial depressant factor released in the blood of endotoxin shocked animals. This was accomplished by utilization of beta adrenergic blockade (propranolol) under the experimental conditions of constant cardiac output and aortic pressure in an isolated canine heart preparation exchanging blood with an intact support animal shocked by endotoxin.

Results from the study fail to reveal a myocardial depressant effect following a lethal injection of endotoxin. Cardiac performance is relatively unimpaired after endotoxin in the presence of beta adrenergic blockade as evidenced by normal cardiac work and power, dP/dT, LVEDP and oxygen uptake. Myocardial performance is postulated to be maintained in the presence of endotoxin and shocked blood by increased coronary blood flow and effective oxyhemoglobin dissociation in an acid medium under conditions of maintained cardiac output and coronary perfusion pressure.

Appreciation is expressed to Susan Owen, Megan Young, R. T. Brantley, Herbert Jennings, Mary Lane, Mary Marple, and Mary Carol Whitaker for technical assistance.

TABLE I. Effect of Endotoxin (LD_{90}) on Intact Support Animal following β Adrenergic Blockade (Mean ± S.E.; N = 6)

Period	Mean Systemic Arterial Pressure (mm Hg)	Heart Rate (min.)
Control	108 (± 7)	158 (± 8)
Post β Adrenergic Blockade (propranolol, 0.5 mg/kg)	89 (± 11)	123 (± 3)
Post Endotoxin (LD_{90}):		
20-30 min.	59 (± 11)	113 (± 4)
50-75 min.	56 (± 5)	130 (± 9)
80-125 min.	33 (± 5)	103 (± 7)

TABLE II. Effect of Endotoxin (LD_{90}) on Hemodynamics of Isolated Heart Preparation following β Adrenergic Blockade (Mean ± S.E.; N = 6)

Period	Mean Aortic (Coronary) Pressure (mm Hg)*	Cardiac Output (cc/min)*	Coronary Blood Temperature*	Coronary Blood Flow (cc/min)	Coronary Vascular Resistance (mm Hg/cc/min)
Control	107 (± 2)	412 (± 9)	38 (± 0.4)	47 (± 5)	2.4 (± 0.3)
Post β Adrenergic Blockade (propranolol, 0.5 mg/kg)	106 (± 2)	418 (± 11)	38 (± 0.6)	55 (± 10)	2.2 (± 0.4)
Post Endotoxin (LD_{90}):					
20-30 min.	106 (± 2)	411 (± 12)	37 (± 0.4)	77 (± 15)	1.7 (± 0.3)
50-75 min.	106 (± 2)	412 (± 7)	37 (± 0.7)	86 (± 12)	1.3 (± 0.1)
80-125 min.	107 (± 3)	443 (± 11)	36 (± 0.9)	110 (± 20)	1.0 (± 0.2)

*Parameters controlled in the experiments.

TABLE III. Effect of Endotoxin (LD_{90}) on Cardiac Performance following β Adrenergic Blockade (Mean ± S.E.; N = 6)

Period	Left Ventricular End Diastolic Pressure (mm Hg)	dP/dT (mm Hg/sec.)	Stroke Work (gm meters)	Heart Rate (/min.)	Power (work/sec.)
Control	+3.8 (± 1.4)	2294 (± 233)	4.3 (± .4)	143 (± 15)	9.7 (± .4)
Post β Adrenergic Blockade (propranolol, 0.5 mg/kg)	+4.5 (± 1.5)	2188 (± 186)	4.9 (± .6)	125 (± 15)	9.6 (± .3)
Post Endotoxin (LD_{90}):					
20-30 min.	+4.4 (± 1.6)	2230 (± 173)	5.0 (± .6)	120 (± 14)	9.4 (± .3)
50-75 min.	+8.5 (± 4.6)	2202 (± 160)	5.1 (± .5)	112 (± 10)	9.1 (± .4)
80-125 min.	+5.0 (± .6)	2248 (± 323)	6.4 (± .8)	100 (± 15)	10.3 (± .5)

TABLE IV. Effect of Endotoxin on pH, Oxygen Uptake, and Carbon Dioxide Production in the Isolated Heart Preparation following β Adrenergic Blockade (Mean ± S.E.; N = 6)

Period	pH*	O_2 Uptake (cc/min/100gms left ventricle)	CO_2 Production (cc/min/100 gms left ventricle)
Control	$\frac{A}{V}$ 7.42 (± .02) / 7.40 (± .02)	9.7 (± 1.3)	9.2 (± 1.4)
Post β Adrenergic Blockade (propranolol, 0.5 mg/kg)	$\frac{A}{V}$ 7.41 (± .03) / 7.38 (± .03)	10.6 (± 1.1)	10.3 (± 1.2)
Post Endotoxin (LD_{90}):			
20-30 min.	$\frac{A}{V}$ 7.30 (± .02) / 7.28 (± .02)	8.8 (± 1.4)	10.9 (± 1.2)
50-75 min.	$\frac{A}{V}$ 7.21 (± .05) / 7.20 (± .05)	11.1 (± 1.0)	7.1 (± .9)
80-125 min.	$\frac{A}{V}$ 7.20 (± .08) / 7.20 (± .08)	9.3 (± 1.7)	6.8 (± 1.8)

* A = Coronary Artery
V = Coronary Vein

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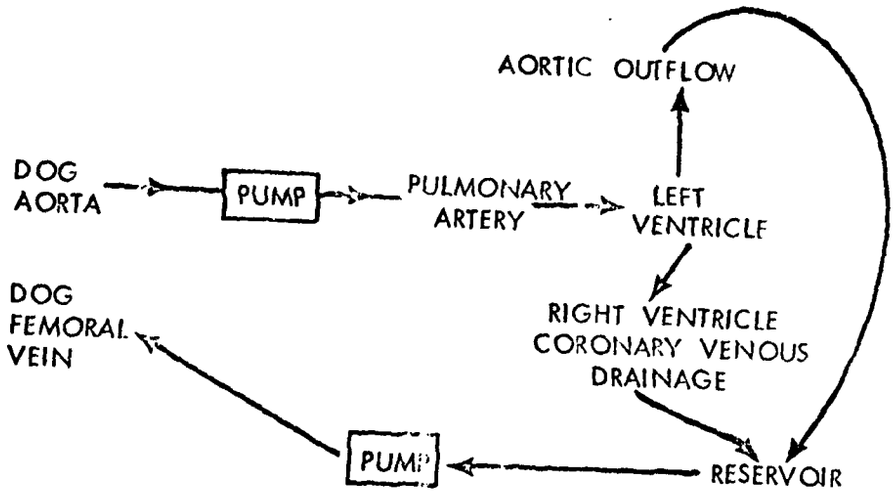
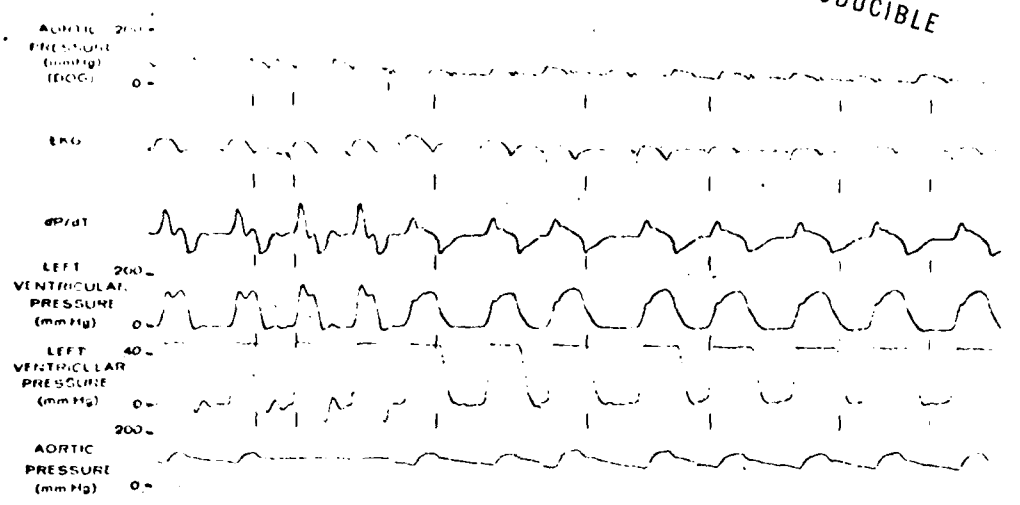


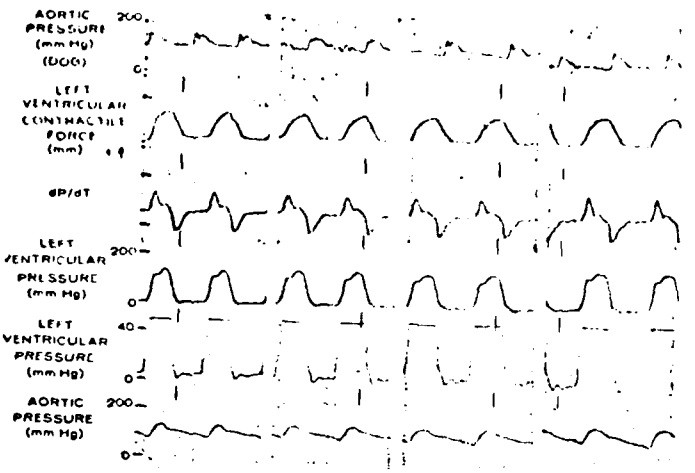
SCHEMATIC DIAGRAM ISOLATED HEART PREPARATION

FIGURE 1 - Schematic diagram of isolated heart preparation.



	Control	1 μg epinephrine	β Adrenergic Blockade	Post-Blockade Control	30 μg epinephrine	Endotoxin LD_{90}	+60 min	10 μg epinephrine
MEAN AORTIC PRESSURE (mm Hg)	103	105		98	95		97	100
LVEDP (mm Hg)	0	+0.5		+1.5	+4.5		+7	+7
CORONARY FLOW (cc/min)	28	36		24	24		62	62
CARDIAC OUTPUT (cc/min)	400	400		432	392		419	419
HEART RATE (beats/min)	105	125		110	90		100	90
dP/dT (mm Hg/sec)	2800	3850		1834	1700		1710	1790

FIGURE 2 - Effects of β adrenergic blockade (propranolol, 0.5 mg/kg) before and after endotoxin on the inotropic, chronotropic and coronary hemodynamic responses of the isolated heart to injected epinephrine (representative experiment). (Note: second record strip, lower frame, mean aortic pressure shown).



	Control	β Adrenergic Blockade	Post-Blockade Control	Endotoxin LD_{90}	+30 min	+60 min
MEAN AORTIC PRESSURE (mm Hg)	100		103		100	97
LVEDP (mm Hg)	+4		+3		+4	+2.5
CORONARY FLOW (cc/min)	36		50		60	65
CARDIAC OUTPUT (cc/min)	386		410		400	400
O_2 UPTAKE (cc/min)	2.5		3.3			3.1
CO_2 PRODUCTION (cc/min)	2.1		2.8			2.2
POWER (work/sec)	.84		.92		.87	.88
dP/dT (mm Hg/sec)	2164		1929		1939	2304

FIGURE 3 - Effects of endotoxin (LD_{90}) on cardiac hemodynamics, work performance and metabolism during β adrenergic blockade (representative experiment).